

Supplementary material

1. Flowcharts of cohort selection

Figure S1: Flow chart of cohort selection for event 1

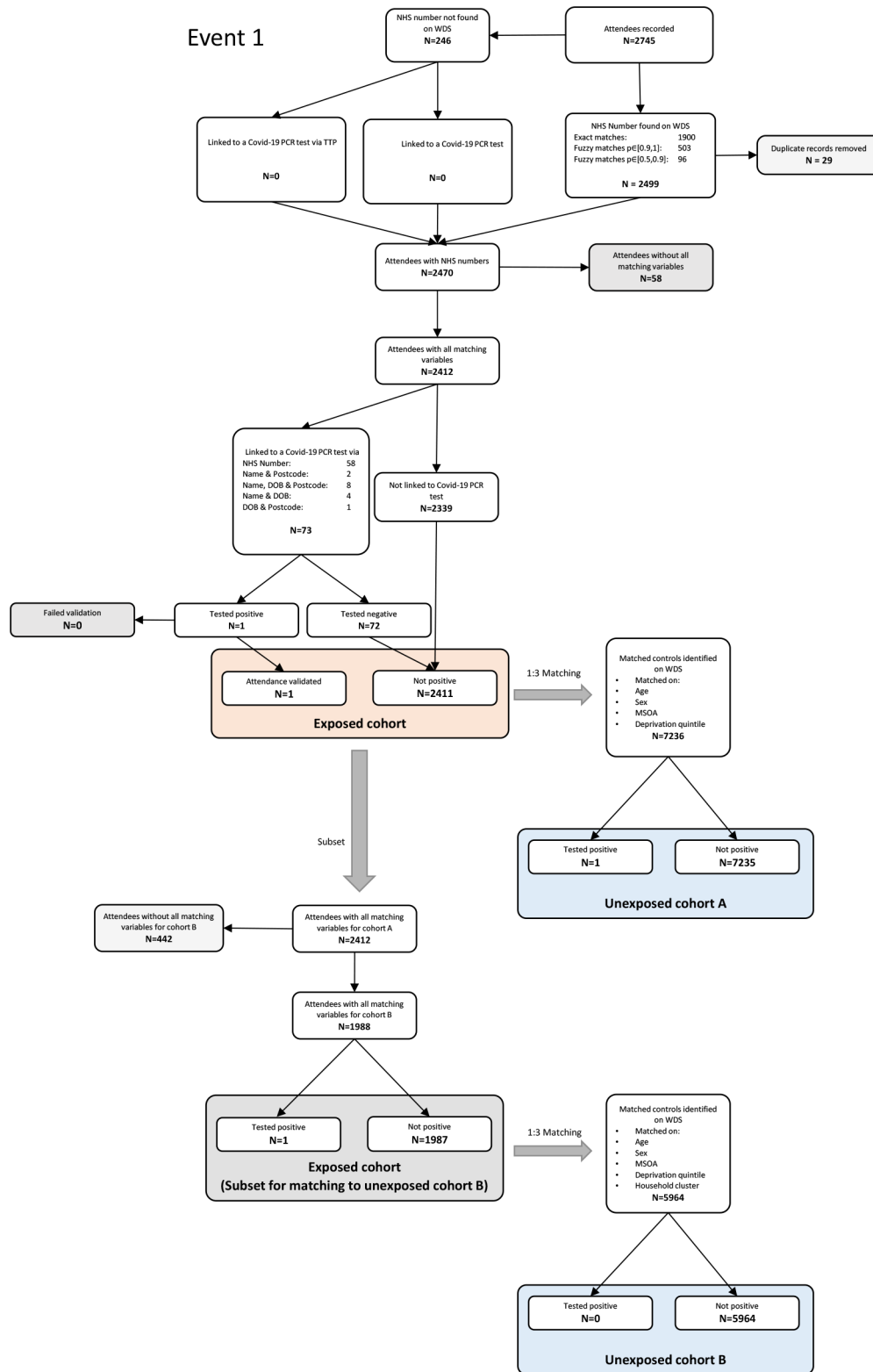
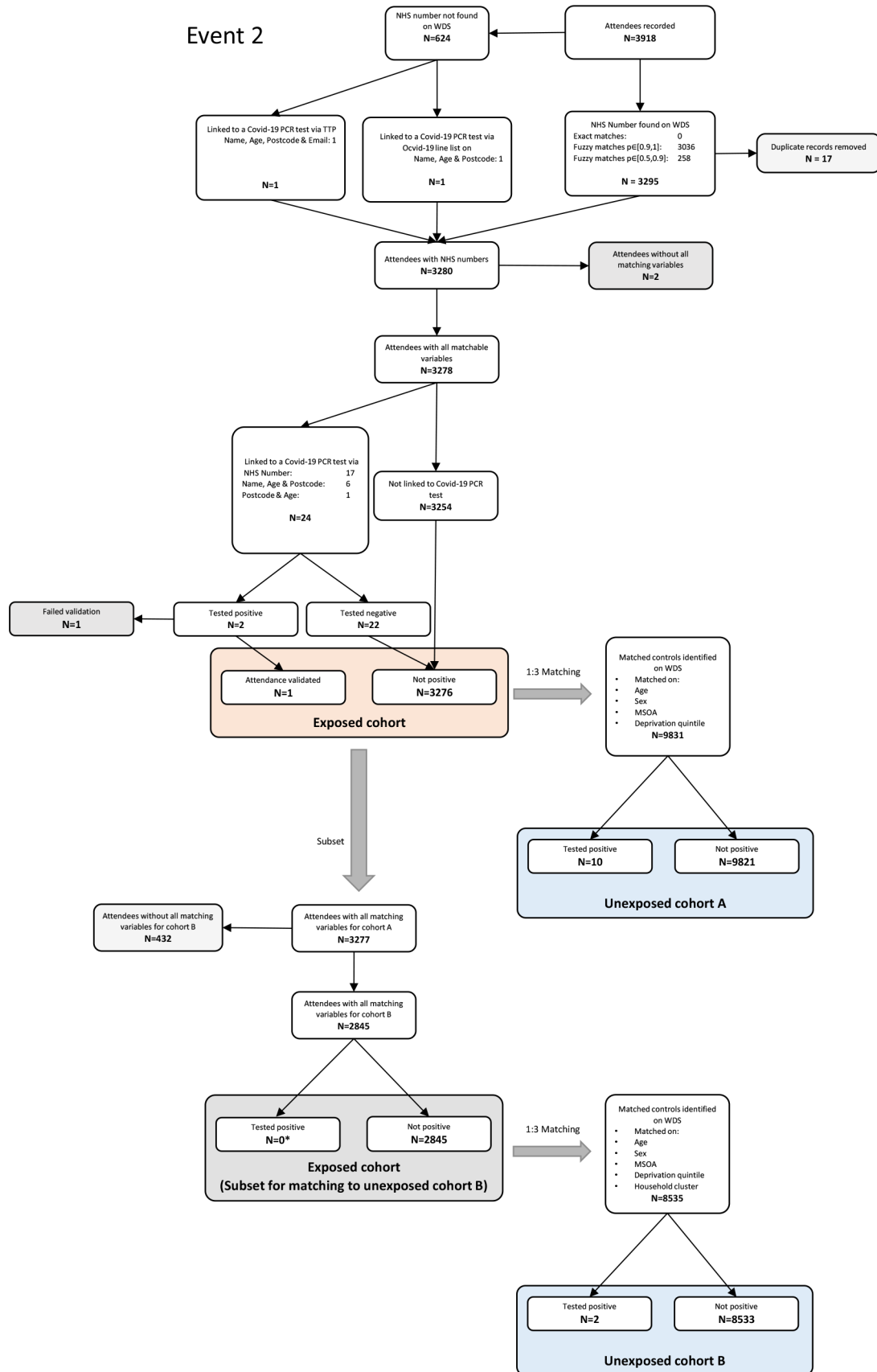


Figure S2: Flow chart of cohort selection for event 2



2. Comparisons between exposed and non-exposed cohorts

The two non-exposed cohorts were tested and their distributions visually inspected to ensure they are equivalent to each other on all match variables. A χ^2 tests comparing distribution of cohorts across the five matching variables (Age, Sex, MSOA, deprivation quintile and household cluster size)

showed that both non-exposed cohorts were not significantly different to the exposed cohort (Table S1).

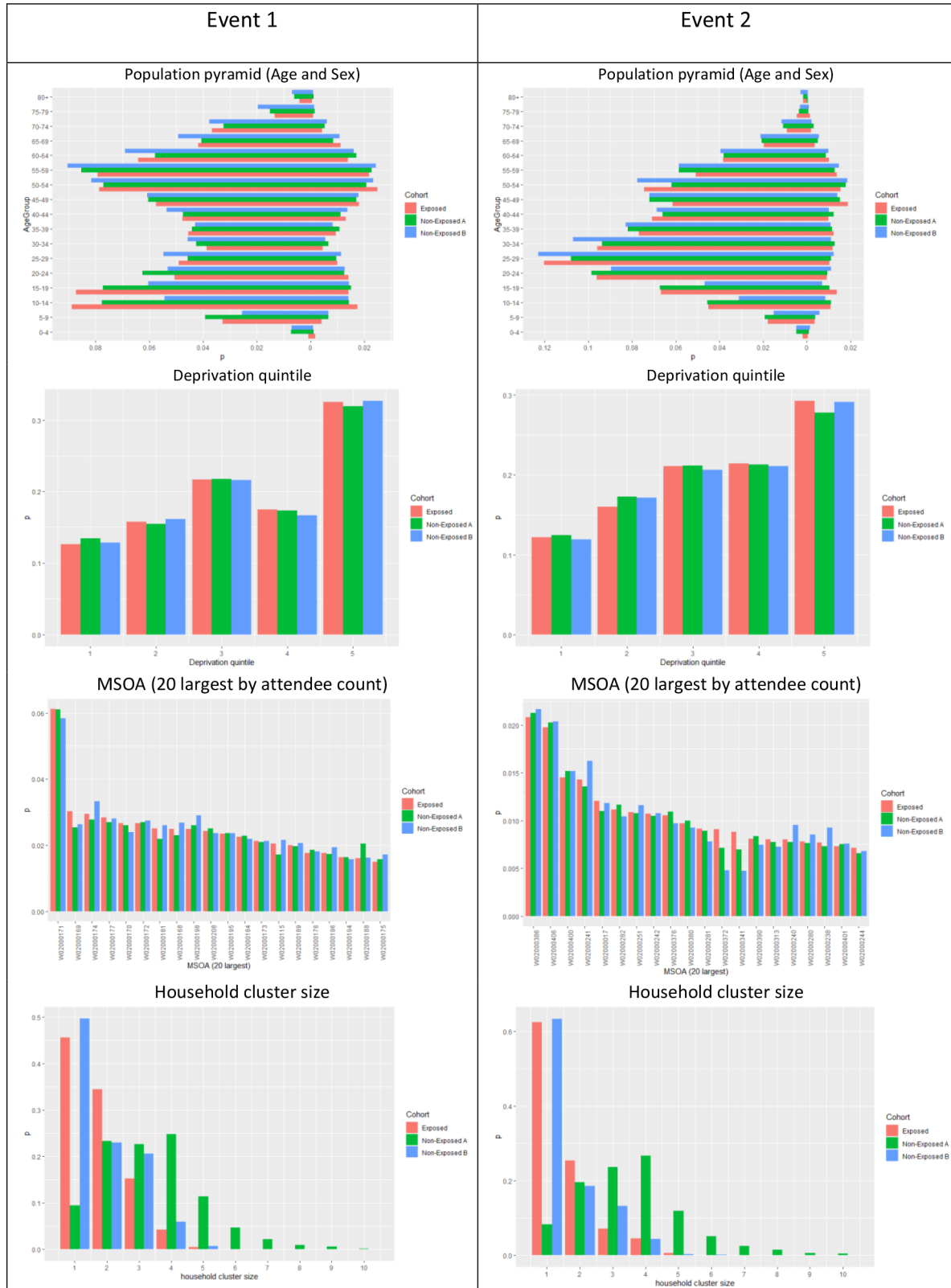
Visual inspection of the distributions of age, sex, deprivation quintile, MSOA and size of household cluster show they are equivalent to other exposed cohorts (Figure S3). Note that non-exposed cohort A was not matched on household cluster, hence the distribution of household cluster size noticeable deviates from that of the exposed cohort, compared to non-exposed cohort B.

Table S1: Results of χ^2 tests comparing exposed cohort to each non-exposed cohort, for each event

	Non-exposed cohort A	Non-exposed cohort B
Event 1	$\chi^2 = 85975$, $df = 39270$, $p < 2.2e-16$	$\chi^2 = 278726$, $df = 46354$, $p > 2.2e-16$
Event 2	$\chi^2 = 466673$, $df = 118090$, $p < 2.2e-16$	$\chi^2 = 449093$, $df = 109515$, $p < 2.2e-16$



Figure S3: Distributions of matching variables for each cohort, for each event



3. Risk analysis without sufficient cases in unexposed cohort B

Using the unexposed cohort B was more problematic due to failure to find cases to include in all groups. A risk ratio

could not be calculated for event 1 due to the absence of any non-exposed cases. Similarly, CLR could not be calculated for unexposed cohort B for either event. An attempt was therefore made to estimate these test statistics using pair-substitutions.

For event 1, RR and CLR were not possible due to no non-exposed cases. A paired substitution was performed on

Table S2: Results of RR and CLR analysis of unexposed cohort B using paired-substitution approximations

Event	Risk ratio and risk difference (95% confidence intervals; significance)	Odds ratio from CLR (95% confidence intervals; significance)
1	RR* = 2.47 (0.15–39.5) RD* = 0.02% (–0.27%–0.66%) $p = 0.57$	OR* = 3.00 (0.19–48.0); $p = 0.44$
2	RR = 1.30 (0.12–14.35) RD = 0.007% (–0.26%–0.33%) $p = 0.81$	OR† = 1.50 (0.14–16.5); $p = 0.74$

*No non-exposed cases were identified for unexposed cohort B. Therefore, an approximation of test statistic was obtained by finding the closest matching non-exposed, non-case in unexposed cohort B, on all possible matching variables to the 1 non-exposed case in unexposed cohort A, and re-labelling them as a case.

†No exposed cases were matchable on all matching variables in unexposed cohort B. Therefore, an approximation of the test statistic was obtained by finding the closest matching exposed non-case, on all possible matching variables, to the 1 exposed case, and re-labelling them as a case.

the one case from unexposed cohort A, for a non-case in unexposed cohort B, which was matched on all possible matching variables (age, sex, MSOA and deprivation quintile). An approximate risk ratio of 2.47 (0.15–39.5) was obtained.

For event 2, CLR was not possible due to no matchable exposed cases. A paired substitution was performed for the one unmatched exposed case for a non-case that is matchable to unexposed cohort B, which was matched on all possible matching variables (age, sex, MSOA and deprivation quintile).

The estimated ORs deviated slightly more from the RRs, compared to unexposed cohort A (see main text): 3.00 (95% CI: 0.19–48.0; $p = 0.44$) for event 1 and 1.50 (95% CI: 0.14–16.5; $p = 0.74$) for event 2. The difference in CLR results may indicate that risk ratios are more subject to matching bias in unexposed cohort B, because of the additional household clustering strategy. However, these results are confounded by the paired-substitution approximation, so direct comparisons between the two sets of results are difficult.

